IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Nathalie BOSC et al. Examiner: Niloofar Rahmani

Serial No.: 10/530,571 Group Art Unit: 1625

Filed: April 7, 2005 Confirmation No.: 8984

Title: METASTABLE BENZOXEPNE DERIVATIVES WHICH CAN BE USED IN THE TREATMENT OF DYSLIPIDAEMIA ATHEROSCLEROSIS AND DIABETES, PHARMACEUTICAL COMPOSITIONS COMPRISING THEM AND PROCESS FOR THE PREPARATION THEREOF

BRIEF ON APPEAL

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed on March 11, 2008, please consider the following:

Payment is made by credit card via EFS to include the fee as set forth under § 41.20(b)(2). The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

(i) REAL PARTY IN INTEREST

The present application is assigned to Merck Patent GmbH, by means of an assignment recorded at reel 017028, frame 0635. Merck Patent GmbH is a wholly owned subsidiary of Merck KGaA, Darmstadt, Germany.

(ii) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

(iii) STATUS OF CLAIMS

Claim 1: allowed.

Claim 2: cancelled.

Claims 3-15: rejected.

Claims 3-15 are all on appeal.

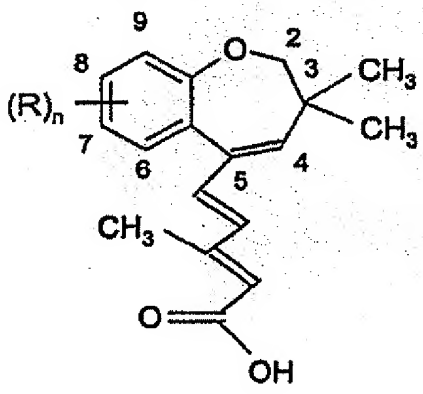
(iv) STATUS OF AMENDMENTS

Appellants' amendment filed January 11, 2008, has *not* been entered.

(v) SUMMARY OF CLAIMED SUBJECT MATTER

There are no independent claims on appeal. Claim 3 recites a process for obtaining the metastable form of a compound of formula I according to claim 1 comprising: a) forming a carboxylic acid salt of the corresponding stable form of a compound of the formula I; b) acidifying an aqueous solution of the salt obtained after step a) until precipitation of the carboxylic acid in its metastable form is obtained. See the specification at page 3, line 4 through page 4, line 31, and particularly page 3, lines 4 through 9.

The invention also involves, in claim 13, pharmaceutical compositions comprising a therapeutically effective amount of a metastable form of a compound of formula I



I

in which n is 1 and R is methoxy, in combination with a pharmaceutically acceptable excipient. See the specification at page 5, line 1 through page 6, line 9, particularly page 6, lines 7-9.

The invention also involves, in claim 14, a method for the treatment of dyslipidaemia, atherosclerosis or diabetes, comprising administering the compound according to claim 1. See the specification at page 8, line 29 through page 9, line 2.

(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Rejection of claims 3-12 and 15 under 35 U.S.C. 112, second paragraph.

Rejection of claims 13 and 14 under 35 U.S.C. 102(b).

Rejection of claims 13 and 14 under 35 U.S.C. 102(e).

Rejection of claims 13 and 14 under the doctrine of obviousness-type double patenting.

(vii) ARGUMENT

Rejection Under 35 U.S.C. 112

Claims 3-12 and 15 are rejected under 35 U.S.C. 112, second paragraph, as it is argued at page 2 of the Final Rejection that there are no steps involved in these method claims. As specifically stated at page 2 of the Final Rejection, "[t]here is no step to form carboxylic acid salt of formula (I) from other compounds." This is submitted to be manifestly untrue.

Claim 3 recites a process for obtaining the metastable form of a compound of formula I, comprising *forming a carboxylic acid salt of the corresponding stable form of a compound of formula I...acidifying an aqueous solution of the salt obtained until... precipitation of the carboxylic acid in its metastable form is obtained.* It is thus manifestly evident that "forming a carboxylic acid salt" and "acidifying" an aqueous solution of said salt are method steps.

It is noted that page 2 of the Final Rejection argues that the product of the first step of the process is a "salt (dry or powder)." Thus, it is believed that there is a fundamental chemical misunderstanding of the process of the present application and claims. To the extent that the Examiner believes that a "salt" must necessarily be a dry product, of course, such an assumption is unsupported in chemistry. It is well known that salts of carboxylic acids can

exist dissolved or suspended in solution. For example, see the attached portion of an introductory college organic chemistry text, noting that carboxylic salts can be dissolved. Moreover, step (b) of the claim recites acidifying an *aqueous solution* of the salt obtained after step (a). Thus, it is clear that the claim encompasses the "steps" of forming a salt and acidifying an aqueous solution of the salt product produced in (a).

Moreover, it is submitted that "forming a carboxylic acid salt", for example, by adding hydroxide ions to the corresponding acid as detailed in the attached organic chemistry text, is manifestly well known to those of skill in the art. Thus, it is submitted that, contrary to the allegations in the Office Action, actual physical steps are recited in the claims, and there is no inconsistency with the Examiner's belief that a dry powder is formed in step (a). Accordingly, ample basis to overturn the § 112 rejection of claims 3-12 and 15 exists, and such is respectfully requested.

Rejections Under 35 U.S.C. 102

Claims 13 and 14 are rejected under 35 U.S.C. 102(b) over Brunet (WO'113).

Claims 13 and 14, through their dependence upon claim 1, require a metastable form of the compound of formula I. Such a metastable form is not disclosed in the commonly assigned reference, as clearly evidenced by the allowance of claim 1 reciting such form. However, it is argued at page 3 of the Final Rejection that claim 13, directed to a "pharmaceutical composition," must necessarily be an aqueous solution, and thus cannot be a metastable material. Again, this analysis is not supported by valid chemistry. For example, at page 7 of the present Specification, solid formulations which are "pharmaceutical compositions" of a metastable compound of formula I are disclosed, including tablets and granules. Moreover, the paragraph bridging pages 7 and 8 discloses a solid composition for oral administration. Example 3 of the specification, at page 13, discloses advantages of the metastable form of the compound of the invention, where that metastable form is prepared as a powder suitable for grinding or micronization. These solid forms - e.g., tablets containing conventional tabletting excipients - are pharmaceutical compositions. Thus, pharmaceutical compositions clearly include solid formulations contrary to

the position in the Office Action. As a result, these claims to the metastable form are in no way anticipated over Brunet, and overturning of the rejection is manifestly required.

Claims 13 and 14 have also been rejected under 35 U.S.C. 102(e) over Brunet (U.S. '758 equivalent to the WO). As discussed above, the reference fails to disclose the subject matter of these claims, and withdrawal of the rejection is also urged.

Double Patenting

Finally, claims 13 and 14 have also been rejected under the doctrine of obviousness-type double patenting over Brunet '758. As discussed above, the reference does not disclose the presently claimed invention, nor suggest it. Overturning of this rejection is also manifestly required.

Respectfully submitted,

/Harry B. Shubin/

Harry B. Shubin, Reg. No. 32,004
Attorney/Agent for Applicant(s)

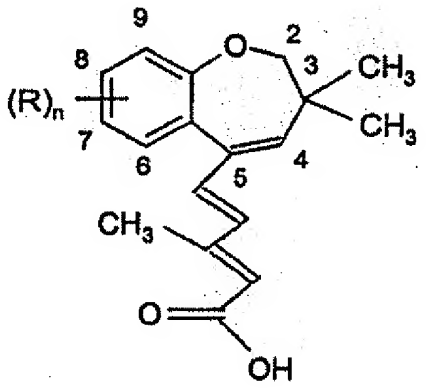
MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

Attorney Docket No.: MERCK-2992

Date: May 12, 2008

(viii) CLAIMS APPENDIX

Claim 1. A metastable form of a compound of formula I:



I

in which

n represents 1 and R, in position 7, represents methoxy, said metastable form having a melting point of 151 to 153°C as measured by differential thermal analysis by scanning between 40 and 180°C at a rate of 10°C/minute, and an X-ray diffraction spectrum defined by the absorption wavelengths in Table I below:

No.	Absorption wavelength (cm-1)	Percentage of transmission (%)	Intensity
1	620.27	0.660	m
2	844.38	0.892	w
3	679.11	0.865	w
4	709.98	0.568	m
5	730.24	0.907	w
6	736.03	0.891	w
7	745.67	0.849	w
8	761.11	0.843	w
9	814.16	0.518	m
10	839.24	0.683	m ;

11	849.85	0.889	w
12	869.15	0.660	m
13	878.79	0.466	s
14	899.05	0.936	w
15	925.10	0.755	m
16	951.14	0.740	m
17	966.58	0.688	m
18	973.33	0.587	m
19	987.80	0.815	w
20	1028.31	0.641	m
21	1046.64	0.517	m
22	1052.43	0.562	m
23	1064.97	0.859	w
24	1128.64	0.825	w
25	1168.19	0.797	w
26	1190.37	0.422	s
27	1199.06	0.408	s
28	1212.56	0.441	s
29	1251.15	0.442	s
30	1270.44	0.254	s
31	1295.52	0.659	m
32	1318.67	0.825	w
33	1355.33	0.769	w
34	1391.98	0.872	w
35	1393.91	0.872	w
36	1413.21	0.651	m
37	1432.50	0.806	w

38	1464.33	0.743	m
39	1494.24	0.511	m
40	1572.37	0.707	m
41	1599.38	0.284	s
42	1623.50	0.810	w
43	1663.05	0.650	m
44	1676.55	0.458	s
45	2837.99	0.863	w
46	2871.75	0.847	w
47	2934.45	0.819	w
48	2960.50	0.818	w
49	3018.38	0.898	w

in which

w means weak intensity,

s means strong intensity, and

m means medium intensity.

Claim 3. A process for obtaining the metastable form of a compound of formula I according to claim 1 comprising:

a) forming a carboxylic acid salt of the corresponding stable form of a compound of the formula I by forming a carboxylic acid salt;

b) acidifying an aqueous solution of the salt obtained after step a) until precipitation of the carboxylic acid in its metastable form is obtained.

Claim 4. The process according to Claim 3, wherein, in a sodium or potassium salt is formed.

Claim 5. The process according to Claim 3, wherein in a), the stable form of the compound of the formula I is reacted with potassium hydroxide or sodium hydroxide.

Claim 6. The process according to Claim 3, wherein, in a), the process is performed in aqueous medium, the stable form of the compound of the formula I initially being in suspension in water.

Claim 7. The process according to Claim 6, wherein, in b), the acidification is performed by the action of hydrochloric acid or sulfuric acid.

Claim 8. The process according to Claim 6, wherein acidification in b) is performed by adding hydrochloric acid or sulfuric acid to the reaction medium.

Claim 9. The process according to claim 3, wherein, in b) acidification is performed with an acid having a concentration between 0.05 M and 10 M.

Claim 10. The process according to claim 3, wherein, in b), the acidification is performed at between 50 and 120°C, and precipitation is performed by cooling the reaction medium.

Claim 11. The process according to Claim 10, wherein precipitation is performed by cooling the reaction medium to between 15 and 40°C.

Claim 12. The process according to claim 3, wherein the stable form of the compound of the formula I is obtained by saponification of the corresponding alkyl ester, followed by acidification, extraction with a water-immiscible solvent, separation of the phases by settling, evaporation and then crystallisation from a solvent which is a lower alkanol, acetonitrile, ethyl acetate, tetrahydrofuran or acetone.

Claim 13. A pharmaceutical composition comprising a therapeutically effective amount of the metastable form of a compound of the formula I according to claim 1, in combination with a pharmaceutically acceptable excipient.

Claim 14. A method for the treatment of dyslipidaemia, atherosclerosis or diabetes, comprising administering a compound according to claim1.

Claim 15. The process according to claim 3, wherein, in b) acidification is performed with an acid having a concentration-between 0.1 and 0.5 M.

(ix) EVIDENCE APPENDIX

The NPL document filed with the Reply on August 6, 2007 is attached hereto.

Third Edition

ORGANIC CHEMISTRY

ROBERT THORNTON MORRISON

ROBERT NEILSON BOYD

New York University

ALLYN AND BACON, INC.

BOSTON
LONDON
SYDNEY
TORONTO

© COPYRIGHT 1973 BY ALLYN AND BACON, INC.
© COPYRIGHT 1966 BY ALLYN AND BACON, INC.
© COPYRIGHT 1959 BY ALLYN AND BACON, INC.
470 ATLANTIC AVENUE, BOSTON

ALL RIGHTS RESERVED

No part of the material protected by this copyright notice may be reproduced or utilized in any form or by any means, electronic or mechanical, including photocopying, recording, or by any informational storage and retrieval system, without written permission from the copyright owner.

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 72-91904

ISBN 0-205-03239-7

Tenth printing . . . . . July, 1976

PRINTED IN THE UNITED STATES OF AMERICA

valeric, and caproic acids; the higher acids have little odor because of their low volatility.

18.4 Salts of carboxylic acids

Although much weaker than the strong mineral acids (sulfuric, hydrochloric, nitric), the carboxylic acids are tremendously more acidic than the very weak organic acids (alcohols, acetylene) we have so far studied; they are much stronger acids than water. Aqueous hydroxides therefore readily convert carboxylic acids into their salts; aqueous mineral acids readily convert the salts back into the carboxylic acids. Since we can do little with carboxylic acids without encountering

$$\underset{\text{Acid}}{\text{RCOOH}} \underset{H^+}{\overset{OH^-}{\rightleftharpoons}} \underset{\text{Salt}}{\text{RCOO}^-}$$

this conversion to and from their salts, it is worthwhile for us to examine the properties of these salts.

Salts of carboxylic acid—like all salts—are crystalline non-volatile solids made up of positive and negative ions; their properties are what we would expect of such structures. The strong electrostatic forces holding the ions in the crystal lattice can be overcome only by heating to a high temperature, or by a very polar solvent. The temperature required for melting is so high that before it can be reached carbon–carbon bonds break and the molecule decomposes, generally in the neighborhood of 300–400°. A decomposition point is seldom useful for the identification of a compound, since it usually reflects the rate of heating rather than the identity of the compound.

The alkali metal salts of carboxylic acids (sodium, potassium, ammonium) are soluble in water but insoluble in non-polar solvents; most of the heavy metal salts (iron, silver, copper, etc.) are insoluble in water.

Thus we see that, except for the acids of four carbons or less, which are soluble both in water and in organic solvents, *carboxylic acids and their alkali metal salts show exactly opposite solubility behavior.* Because of the ready interconversion of acids and their salts, this difference in solubility behavior may be used in two important ways: for *identification* and for *separation.*

A water-insoluble organic compound that dissolves in cold dilute aqueous sodium hydroxide must be either a carboxylic acid or one of the few other kinds of organic compounds more acidic than water; that it is indeed a carboxylic acid can then be shown in other ways.

$$\underset{\substack{\text{Stronger acid}\\ \textit{Insoluble in } H_2O}}{\text{RCOOH}} + \text{NaOH} \longrightarrow \underset{\substack{\textit{Soluble in } H_2O}}{\text{RCOONa}} + \underset{\text{Weaker acid}}{H_2O}$$

Instead of sodium hydroxide, we can use aqueous sodium bicarbonate; even if the unknown is water-soluble, its acidity is shown by the evolution of bubbles of CO_2.

$$\underset{\textit{Insoluble in } H_2O}{\text{RCOOH}} + \text{NaHCO}_3 \longrightarrow \underset{\textit{Soluble in } H_2O}{\text{RCOONa}} + H_2O + CO_2\uparrow$$

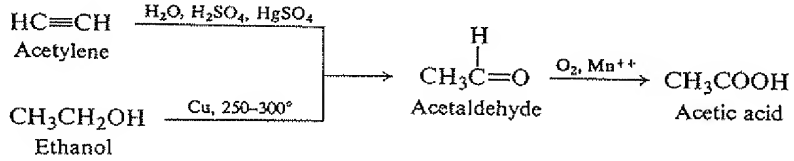
We can separate a carboxylic acid from non-acidic compounds by taking advantage of its solubility and their insolubility in aqueous base; once the separation has been accomplished, we can regenerate the acid by acidification of the aqueous solution. If we are dealing with solids, we simply stir the mixture with aqueous base and then filter the solution from insoluble, non-acidic materials; addition of mineral acid to the filtrate precipitates the carboxylic acid, which can be collected on a filter. If we are dealing with liquids, we shake the mixture with aqueous base in a separatory funnel and separate the aqueous layer from the insoluble organic layer; addition of acid to the aqueous layer again liberates the carboxylic acid, which can then be separated from the water. For completeness of separation and ease of handling, we often add a water-insoluble solvent like ether to the acidified mixture. The carboxylic acid is extracted from the water by the ether, in which it is more soluble; the volatile ether is readily removed by distillation from the comparatively high-boiling acid.

For example, an aldehyde prepared by the oxidation of a primary alcohol (Sec. 16.8) may very well be contaminated with the carboxylic acid; this acid can be simply washed out with dilute aqueous base. The carboxylic acid prepared by oxidation of an alkylbenzene (Sec. 12.10) may very well be contaminated with unreacted starting material; the carboxylic acid can be taken into solution by aqueous base, separated from the insoluble hydrocarbon, and regenerated by addition of mineral acid.

Since separations of this kind are more clear-cut and less wasteful of material, they are preferred wherever possible over recrystallization or distillation.

18.5 Industrial source

Acetic acid, by far the most important of all carboxylic acids, is prepared by air oxidation of acetaldehyde, which is readily available from the hydration of acetylene (Sec. 8.13), or the dehydrogenation of ethanol.



Large amounts of acetic acid are also produced as the dilute aqueous solution known as *vinegar*. Here, too, the acetic acid is prepared by air oxidation; the compound that is oxidized is ethyl alcohol, and the catalysts are bacterial (*Acetobacter*) enzymes.

The most important sources of aliphatic carboxylic acids are the animal and vegetable **fats** (Secs. 33.2–33.4). From fats there can be obtained, in purity of over 90%, straight-chain carboxylic acids of even carbon number ranging from six to eighteen carbon atoms. These acids can be converted into the corresponding alcohols (Sec. 18.18), which can then be used, in the ways we have already studied (Sec. 16.10), to make a great number of other compounds containing long, straight-chain units.

The most important of the aromatic carboxylic acids, **benzoic acid** and the

(x) RELATED PROCEEDINGS APPENDIX

None.